Noncorticosteroid Immunosuppression Limits Myocardial Damage and Contractile Dysfunction in Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss Syndrome)

Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome) is a rare, systemic, small- to medium-sized vessel necrotizing vasculitis. The disease is characterized by common cardiac involvement, which remains the major determinant of mortality (1). Glucocorticoids and noncorticosteroid immunosuppressants are the cornerstones of therapy for this disease; they inhibit the inflammatory process, prevent organ damage, enhance survival, and reduce the relapse rate. Glucocorticoids are the first-line agents in all patients with EGPA, whereas adjunctive noncorticosteroid immunosuppressants are reserved only for the most severe, life-threatening disease. To date, the impact of noncorticosteroid immunosuppression on cardiac involvement in patients with EGPA is poorly defined and it remains unknown whether such therapy can prevent heart damage. Therefore, we hypothesized that the addition of noncorticosteroid immunosuppressants to glucocorticoids may effectively limit myocardial damage and contractile dysfunction in patients with EGPA.

Of the 65 patients with EGPA diagnosed and treated at 4 tertiary centers from 1990 to 2013, identified in the Vasculitis Registry of Jagiellonian University Medical College, 51 patients with clinical remission (Birmingham Vasculitis Activity Score = 0 in last 3 months), complete medical data, no severe valve dysfunction, and no contraindication to magnetic resonance and/or gadolinium contrast were enrolled in this study. Baseline (demographic, clinical, laboratory, transthoracic echocardiography) data on disease presentation and course as well as therapeutic data on month-by-month treatment were retrospectively collected. All patients were scheduled for follow-up, including cardiac magnetic resonance to assess left ventricular ejection fraction (LVEF) and myocardial damage depicted by late gadolinium enhancement (LVLGE). Adverse cardiac events were defined as cardiac death and/or hospitalization due to decompensated heart failure.

At diagnosis, 15 (29%) patients demonstrated cardiac involvement. In addition at diagnosis, 49 (96%), 28 (55%), 28 (55%), 9 (18%), and 8 (16%) presented with lung, peripheral nervous system, skin, gastrointestinal tract, and kidney involvement, respectively. Of those with heart involvement, all patients presented with heart failure, 2 patients had suspected acute coronary syndrome with obstructive coronary atherosclerosis excluded by coronary angiography, 1 patient had sudden cardiac arrest with successful resuscitation, 5 patients had myocarditis, 4 patients had perimyocarditis, and 1 patient had pericarditis. Coronary angiography was normal in all subjects with myocarditis or perimyocarditis. Baseline transthoracic echocardiography at diagnosis showed an LVEF of 56.1 ± 12.9%, and 13 (25%) patients had an LVEF <50%. At diagnosis, all patients received glucocorticoids; 18 (35%) patients received additional noncorticosteroid immunosuppression (16 patients received cyclophosphamide, 1 patient received methotrexate, and 1 patient received cyclosporine). During the disease course, 21 (41%) patients experienced clinical relapse(s). Because of relapse, 6 (12%) patients received an additional noncorticosteroid immunosuppressant (3 patients received cyclophosphamide, 2 patients received azathioprine, and 1 patient received methotrexate). During disease course, 28 (55%) patients received angiotensin-converting enzyme inhibitors, 25 (49%) patients received beta-blockers, 7 (14%) patients received mineralocorticoid receptor antagonists, 1 (2%) patient received an angiotensin receptor blocker, and 1 (2%) patient received a calcium blocker. At follow-up, all patients received low-dose glucocorticoids, 7 patients (14%) received cyclophosphamide, 3 (6%) patients received azathioprine, and 1 (2%) patient received methotrexate.

Follow-up was performed 39.2 ± 38.7 months after EGPA was diagnosed. At follow-up, all patients were in clinical remission, 29 (57%) patients had cardiac involvement, 25 (49%) patients had heart failure, and none had symptoms of angina. At follow-up, 49 (96%), 30 (59%), 28 (55%), 14 (27%), 10 (20%), and 4 (8%) had history of lung, peripheral nervous system, skin, kidney, gastrointestinal tract, and central nervous system involvement, respectively. After diagnosis of EGPA, noncorticosteroid immunosuppressants were administered for 8.2 ± 13.1 months, representing 25.6 ± 33.2% of disease duration. No patients died after diagnosis, but 10 (20%) patients were hospitalized due to decompensated heart failure. When comparing subjects in whom noncorticosteroid immunosuppressants were and were not initiated at diagnosis, the latter more frequently presented with new onset or progression (increase in New York Heart Association functional class ≥1) of heart failure (1 [6%] vs. 12 [36%]; p = 0.02) and required hospitalization due to decompensated heart failure (0 [0%] vs. 10 [30%];

TABLE 1 Study Group Characteristics and Unadjusted Predictors of Left Ventricular Myocardial Damage (Late Gadolinium Enhancement) and Systolic Dysfunction (Ejection Fraction <50%) at Follow-Up

Parameter	All Patients (n = 51)	Left Ventricular Myocardial Damage at Follow-Up		Left Ventricular Systolic Dysfunction at Follow-Up	
		Present (n = 29) / Absent (n = 22)	OR (95% CI)	Present (n = 22) / Absent (n = 29)	OR (95% CI)
Baseline					
Male	15 (29)	8 (28)/7 (32)	0.82 (0.24–2.74)	5 (23)/10 (34)	0.56 (0.16–1.97)
Age at diagnosis, yrs	41.2 ± 14.8	39.8 ± 14.5/43.1 ± 15.3	0.99 (0.94–1.02)	37.9 ± 11.9/43.7 ± 16.4	0.97 (0.93–1.01)
Five-factor score at diagnosis >0	19 (37)	14 (48)/5 (23)	3.17 (0.92–10.90)	11 (50)/8 (28)	2.63 (0.82–8.43)
Heart failure at diagnosis	15 (29)	13 (45)/2 (9)*	8.13 (1.60–41.36)*	11 (50)/4 (14)*	6.25 (1.63–24.02)*
NYHA functional class at diagnosis, none/1/2/3/4	36/3/5/5/2	16/2/4/5/2 / 20/1/1/0/0	1.93 (1.03–3.62)*	11/1/3/5/2 / 25/2/2/0/0*	2.01 (1.15–3.53)*
Heart involved† at diagnosis	15 (29)	13 (45)/2 (9)*	8.13 (1.60–41.36)*	11 (50)/4 (14)*	6.25 (1.63–24.02)*
LVEF <50% at diagnosis	13 (25)	12 (41)/1 (5)*	14.82 (1.75–125.73)*	11 (50)/2 (7)*	13.50 (2.56–71.13)*
History of myocarditis	13 (25)	12 (41)/1 (5)*	14.82 (1.75–125.73)*	9 (41)/4 (14)*	4.33 (1.12–16.78)*
History of pericarditis	13 (25)	11 (38)/2 (9)*	6.11 (1.19–31.37)*	8 (36)/5 (17)	2.74 (0.75–10.04)
ANCA present	11 (22)	4 (14)/7 (32)	0.34 (0.09–1.37)	2 (9)/9 (31)	0.22 (0.04–1.16)
Maximum blood eosinophil count, 10^2 cells/μl	78.0 ± 47.1	88.3 ± 47.9/64.4 ± 43.3	1.01 (1.00–1.03)	91.8 ± 52.7/67.5 ± 40.2	1.01 (0.99–1.03)
Medical therapy					
Noncorticosteroid immunosuppressant					
Not introduced	27 (53)	19 (66)/8 (36)	3.33 (1.04–10.59)*	16 (73)/11 (38)*	4.36 (1.31–14.51)*
Not introduced at diagnosis	33 (65)	24 (83)/9 (41)*	6.93 (1.92–25.06)*	19 (86)/14 (48)*	6.79 (1.64–28.04)*
Duration of therapy, months	0.0 (0.0–10.0)	0.0 (0.0–9.3)/6.5 (0.0–18.0)	0.95 (0.90–1.00)*	0.0 (0.0–13.6)/6.0 (0.0–17.3)	0.95 (0.89–1.01)
Therapy discontinuity index‡, %	100.0 (44.4–100.0)	100.0 (80.6–100.0)/ 57.7 (26.1–100.0)*	1.03 (1.01–1.05)*	100.0 (86.4–100.0)/64.3 (31.5–100.0)*	1.03 (1.01–1.06)*
Cyclophosphamide					
Not introduced	32 (63)	21 (72)/11 (50)	2.63 (0.82–8.43)	17 (77)/15 (52)	3.17 (0.92–10.91)
Not introduced at diagnosis	35 (69)	24 (83)/11 (50)*	4.80 (1.34–17.19)*	19 (86)/16 (55)*	5.15 (1.24–21.30)*
Duration of therapy, months	0.0 (0.0–6.0)	0.0 (0.0–5.0)/0.0 (0.0–12.0)	0.94 (0.88–1.01)	0.0 (0.0–0.0)/0.0 (0.0–9.3)	0.95 (0.87–1.03)
Therapy discontinuity index‡, %	100.0 (78.8–100.0)	100.0 (87.8–100.0)/100.0 (44.4–100.0)	1.02 (1.00–1.05)*	100.0 (100.0–100.0)/100.0 (45.7–100.0)	1.03 (1.00–1.06)*
Corticosteroids					
Introduced	51 (100)	29 (100)/22 (100)	–	22 (100)/29 (100)	–
Daily dose§ at remission, mg	7.1 ± 2.2	6.8 ± 2.2/7.5 ± 2.2	0.88 (0.68–1.13)	7.0 ± 2.4/7.2 ± 2.0	0.96 (0.75–1.25)
Cardiovascular agents					
Beta-blocker	25 (49)	18 (62)/7 (32)	3.04 (0.95–9.71)	14 (64)/11 (38)	2.36 (0.76–7.34)
Angiotensin-converting enzyme inhibitor	28 (55)	20 (69)/8 (36)*	3.89 (1.21–12.55)*	14 (64)/14 (48)	1.88 (0.60–5.83)
Mineralocorticoid receptor antagonist	7 (14)	7 (24)/0 (0)*	–	6 (27)/1 (7)*	10.50 (1.16–95.17)*
Follow-up					
Heart failure	25 (49)	24 (83)/1 (5)*	100.80 (10.89–933.19)*	21 (95)/4 (14)*	131.25 (13.6–1,266.37)*
NYHA functional class, none/1/2/3/4	26/13/6/6/0	5/12/6/6/0 / 21/1/0/0/0*	51.61 (5.55–479.79)*	1/10/5/6/0 / 25/3/1/0/0*	23.17 (4.36–123.12)*
Q-wave in electrocardiogram	11 (22)	11 (38)/0 (0)*	–	10 (45)/1 (3)*	23.33 (2.68–203.14)*

Values are n (%), mean ± SD, or median (interquartile range). *p < 0.05. †Defined as: 1) heart failure; 2) life-threatening cardiac arrhythmia including complete atrioventricular block, sustained ventricular tachycardia; and/or cardiac arrest; 3) electrocardiogram and/or laboratory evidence of myocardial damage; or 4) imaging evidence of myocardial and pericardial involvement, if non-vasculitis causes were excluded. ‡Defined as nontreatment to overall disease duration ratio. §Expressed as equivalent of methylprednisolone.

ANCA = antineutrophil cytoplasmic antibodies; CI = confidence interval; LVEF = left ventricular ejection fraction; NYHA = New Your Heart Association functional class; OR = odds ratio.

p = 0.009), with shorter adverse cardiac event-free survival (p = 0.049 for log-rank test comparison).

At follow-up, linear regression revealed the association of LVEF with LVLGE volume (β = −1.03; p < 0.001) and LVLGE index (β = −1.26; p < 0.001), defined as LVLGE volume to myocardial volume ratio. In the subgroup of patients without cardiac involvement at diagnosis, LVLGE was less frequently observed in those with (n = 13) than those without (n = 23) noncorticosteroid immunosuppression initiated at diagnosis (1 [8%] vs. 15 [65%]; p = 0.001). Interestingly, LVEF was similar at the time of diagnosis and follow-up (58.3 ± 14.1% vs. 56.8 ± 14.2%; p = 0.30) or decreased from the time of diagnosis to follow-up (54.8 ± 12.3% vs. 49.9 ± 17.7%; p = 0.02) when noncorticosteroid immunosuppression was or was not introduced at diagnosis, respectively.

Table 1 provides unadjusted association of baseline and therapeutic data with LVLGE and LVEF <50% at follow-up. Of baseline data, myocarditis (odds ratio [OR]: 14.82; 95% confidence interval [CI]: 1.75 to 125.73; p = 0.01; chi-square: 10.4; area under the curve [AUC]: 0.68) and LVEF <50% at diagnosis (OR: 13.50; 95% CI: 2.56 to 71.13; p = 0.002; chi-square: 12.9; AUC: 0.72) were the only independent determinants of LVLGE and LVEF <50% at follow-up, respectively. Importantly, noncorticosteroid immunosuppression yielded an association with LVLGE and LVEF <50% at follow-up (**Table 1**). Using sequential logistic regression analysis for prediction of LVLGE and LVEF <50% at follow-up, the lack of introduction of noncorticosteroid immunosuppression at diagnosis (chi-square: 24.8 and AUC: 0.83 for prediction of LVLGE; chi-square: 23.3 and AUC: 0.84 for prediction of LVEF <50%) and noncorticosteroid immunosuppression discontinuity index, defined as nontreatment to overall disease duration ratio (chi-square: 19.1 and AUC: 0.82 for prediction of LVLGE; chi-square: 19.6 and AUC: 0.84 for prediction of LVEF <50%), provided incremental prognostic value over baseline data (all p < 0.05 for increase in global chi-square and AUC of receiver-operating characteristics between observed binary outcome and predicted probabilities from regression models). The effect was unchanged when data on standard treatment of heart failure (i.e., use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists) were included in the analysis. In addition, after adjustment for age, number of relapses, and maximum level of blood eosinophilia, the extent of myocardial damage at follow-up expressed as LVLGE volume was associated with duration of noncorticosteroid immunosuppression (β = −0.28; p = 0.03) or noncorticosteroid immunosuppression discontinuity index (β = 0.13; p = 0.008).

Accordingly, the data indicate that the lack of or inadequate duration of noncorticosteroid immunosuppression appear to be independent determinants of cardiac involvement in EGPA and the extent of myocardial damage is associated with insufficient duration of noncorticosteroid immunosuppression. We believe that noncorticosteroid immunosuppression has the potential to limit myocardial damage and deterioration of LV systolic function and should be regarded as an effective strategy for preventing heart failure in patients with EGPA.

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Delegation of Duties and Professional Standards

I read with interest the letter from Drew et al. (1), which commented on the suspected shrinking pool of cardiologists who are willing and able to read the standard 12-lead electrocardiogram. They suggested that nurse practitioners should be trained to perform